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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/808,004	03/24/2004	Mary L. Owens	67059(54610)	4652

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	**PAPER NUMBER**
1642	
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07/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/808,004	Applicant(s) OWENS ET AL.	
	Examiner Brandon J. Fetterolf, PhD	Art Unit 1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 15 June 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *6* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *15 June 2007*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☒ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1 and 7-16*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☒ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). 6/15/2007
13. ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 6/15/2007 in response to the previous Final Office Action (12/15/2006) is acknowledged, but has not been entered. The amendment has not been entered because the amendment is not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal. For example, the amendment adds nineteen new claims which incorporate subject matter which was not previously considered or searched, e.g., claims 27-29 recitiation of 5% IRM compound; and further, includes limitations of finally rejected claims.

Claims 1 and 7-16 are currently pending and under consideration.

Information Disclosure Statement

The Information Disclosure Statement filed on 6/15/2007 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

Rejections Maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 7-12 and 16 **remain** rejected under 35 U.S.C. 103(a) as being unpatentable over Marks et al. (J. Am. Acad. Dermatol. 2001; 44: 807-813, IDS) or Beutner et al. (J. Am. Acad. Dermatol. 1999; 41: 1002-1007, IDS) or Kagy et al. (Dermatol. Surg. 2000; 26: 577-579).

Marks et al teach a method of treating superficial basal cell carcinoma comprising administering an effective amount of imiquimod 5% cream. With regards to the administration cycle, the reference teaches that nine patients were randomized to 6 weeks' application of iminquimod in 1 of the 4 treatment cycles: twice every day, once every day, twice daily 3 times/week, once daily 3 times/week (page 807, *Methods*). Moreover, Marks et al. teach that 100% of the twice daily treatment cycle had hisological clearance, 87.9 % clearance in the once every day regimen, 73.3% clearance in the twice daily 3 times/week regiment, and 69.7% clearance in the once-daily 3 times/week treatment cycle.

Beutner et al. teach a method of treating basal cell carcinoma comprising administering an effective amount of imiquimod 5% cream. With regards to the administration, the reference teaches that 24 patients were treated for at least 6 weeks following 1 of the 5 treatment cycles: twice daily, once per day, three times weekly, twice weekly and once weekly (page 1003, 2nd column, *Study Results*). Moreover, Beutner et al. teach that 100% of the twice daily treatment cycle had complete clearance, 100% of the once daily, 100% of the three times weekly, 60% of the twice weekly and 50% of the once weekly (page 1004, 1st column, Table II).

Kagy et al. teach a method of treating superfacial basal cell carcinomas comprising administering an effective amount of imiquimod 5% cream. With regards to the administration, the reference teaches that one patient was treated for 18 weeks with a once daily application of 5% imiquimod cream, wherein after the 18th week the superfacial truncal BCC appeared to be eradicated (page 577, Top section, *METHODS* and page 578, 1st column, 1st full paragraph). In a commentary by John Geisse, the reference teaches that what remains to be defined for imiquimod treatment is the optimal dosing in which there can be three variables: concentration, which at the present time is fixed at 5% by available formulation, the frequency of application, and the duration of course of the therapy (page 578, 1st column, 4th paragraph of *Commentary*). With regards to the duration of therapy, the reference teaches that the optimal duration would be five out of seven days per week with duration of therapy of about 12 weeks (page 579, 1st column, last paragraph). Lastly, the reference

teaches that further clinical trials are needed to determine the optimal dosing to minimize cutaneous side-effects and maximize efficacy (page 579, 2nd column, paragraph bridging 1st column).

Marks et al., Beutner et al. and Kagy et al. do not explicitly teach a treatment cycle that comprises at least two consecutive days or at least five consecutive days in which imiquimod is administered and at least one day or 2 days in which imiquimod is not administered. Nor do Marks et al., Beutner et al. and Kagy et al. explicitly teach that the treatment area further comprises skin at least 0.5 cm beyond the margin of the lesion.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to optimize the treatment cycle and treatment area for the administration of imiquimod as taught by Marks et al., Beutner et al. and Kagy et al.. One would have been motivated to do so because while each of the references teach successful treatments of basal cell carcinoma, Geisse et al. (Commentary in Kagy et al.) teaches that further clinical trials are needed to determine the optimal dosing to minimize cutaneous side-effects and maximize efficacy. Furthermore, the Courts have found that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. As such, one would have a reasonable expectation of success that by optimizing the treatment cycle or treatment area of imiquimod to at least 2 or 5 days administration of imiquimod and at least one or two days of "rest" and at least 0.5 cm beyond the margin of the lesion, one would achieve an optimal method of treating basal cell carcinoma which minimizes the cutaneous side-effects.

Note: In order to expedite prosecution, the Examiner would like to address Applicants arguments pertaining to the instant rejection. The majority of Applicants arguments pertain to the unexpected results of the present invention (see Remarks, page 8, 9, 10 and 12 for example). In particular, Applicants contend that the rest days of the prior art were a result of adverse reaction, not as a means of preventing, reducing, or ameliorating the adverse reactions.

These arguments have been carefully considered, but are not found persuasive.

In the instant case, while the Examiner acknowledges Applicants assertions of unexpected results, the Examiner recognizes that the arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit

or declaration include statements regarding **unexpected results**, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant (emphasis added).

Claims 13-15 **remain** rejected under 35 U.S.C. 103(a) as being unpatentable over Marks et al. (J. Am. Acad. Dermatol. 2001; 44: 807-813) or Beutner et al. (J. Am. Acad. Dermatol. 1999; 41: 1002-1007) or Kagy et al. (Dermatol. Surg. 2000; 26: 577-579) in view of Aldara™ (FDA, Labeling Revision 2001).

Marks et al., Beutner et al. and Kagy et al. teach, as applied to claims 1, 7-12 and 16 above, a method of treating basal cell carcinomas comprising administering an effective amount of imiquimod 5% cream.

Marks et al., Beutner et al. and Kagy et al. do not explicitly teach that the imiquimod cream is applied to the treatment are for about eight hours.

Aldara™ teaches that Aldara™ is the brand name for imiquimod which is an immune response modifier used for the treatment of external genital and perianal warts/condyloma acuminate in adults (page 3 and page 6, Indication and Usage). The labeling revision further teaches (page 12, Dosage and Administration) that Aldara cream should be applied to the target area prior to normal sleeping hours, and left on the skin for 6 to 10 hours.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to apply the imiquimod cream to the treatment area as taught by Marks et al., Beutner et al. and Kagy et al. for about 8 hours in order to optimize the treatment cycle and treatment area for the administration of imiquimod. One would have been motivated to do so because the Aldara labeling revision teaches (page 12, Dosage and Administration) that Aldara cream should be applied to the target area prior to normal sleeping hours, and left on the skin for 6 to 10 hours. As such, one would have a reasonable expectation of success that by applying the imiquimod cream to the treatment area as taught by Marks et al., Beutner et al. and Kagy et al. for about 8 hours, one would achieve the optimal time for imiquimod treatment of basal cell carcinoma.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

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